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Original Article

The use of weekly topotecan in the treatment of heavily pretreated recurrent epithelial ovarian and primary peritoneal cancer: The Kaohsiung Chang Gung experience

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ABSTRACT

Objective: We attempted to investigate the safety and efficacy of alternative weekly topotecan dosing in a heavily pretreated Taiwanese population with recurrent epithelial ovarian cancer (EOC) and primary peritoneal carcinoma (PPC).

Materials and methods: We retrospectively reviewed the medical records of patients with recurrent EOC and PPC who had been treated with weekly topotecan between November 2008 and May 2012. Topotecan was given at a dose of 2.75–4 mg/m^2 via a 30-minute intravenous (IV) infusion on Days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity occurred.

Results: Thirty-two patients were identified and 24 (75%) of them had received at least two previous regimens of chemotherapy; the median number of treatment courses was seven. The main toxicities (Grades 3 and 4) were anemia in seven (21.9%), neutropenia in six (18.8%), and thrombocytopenia in two patients (6.2%). No deaths were attributable to the therapy. Overall, seven patients (21.9%) showed a partial response (PR), while seven patients (21.9%) with stable disease (SD) were observed. Furthermore, we found a favorable response and toxicity profile in patients who received the lowest dose intensity (2.75 mg/m^2). The median progression-free survival (PFS) and overall survival (OS) were 3 months [95% confidence interval (CI) 2.7–3.2] and 20 months (95% CI 11.1–28.9), respectively.

Conclusion: Topotecan administered as a weekly dosage (2.75–4 mg/m^2) seems to be a tolerable regimen with modest activity in a Taiwanese population. Although the lower dose schedule showed a higher response with a better toxicity profile, further studies with more cases are needed to confirm this finding.

Introduction

Epithelial ovarian cancer (EOC) continues to be the leading cause of death among women with gynecologic malignancies and the 10th leading cause of cancer death in women in Taiwan [1]. Because no effective strategy exists for screening of ovarian cancer, most of the patients were diagnosed with advanced-stage diseases. Surgical cytoreduction combined with platinum and taxane chemotherapy is the currently preferred initial management for women with Stage III or Stage IV EOC. Most patients, however, will experience recurrence and only about 10–45% survive for 5 years [2]. Primary peritoneal carcinoma (PPC) behaves in a manner similar to that of EOC. For patients with platinum-sensitive tumors upon relapse, platinum-doublet agents may be selected for salvage treatment; however, for those with platinum-refractory or platinum-resistant tumors, the nonplatinum single-agent treatment options are recommended, including docetaxel, etoposide, gemcitabine, pegylated liposomal doxorubicin, and topotecan [3].

Topotecan (Hycamtin; GlaxoSmithKline, Philadelphia, PA, USA), a topoisomerase I inhibitor, is a valid and widely used second-line therapeutic approach for recurrent EOC and PPC, both in patients with platinum-sensitive and platinum-resistant disease. The

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approved topotecan dosing by the Food and Drug Administration (FDA) in 1996 and many other Western countries is a 1.5 mg/m^2/d intravenous (IV) infusion over 30 minutes on Days 1–5 of a 3-week schedule. The response rates were reported to be 19–33% for platinum-sensitive disease and 14–18% for platinum-resistant disease. Although the regimen demonstrates significant antitumor activity, high morbidity associated with Grade 3/4 myelosuppression, fatigue, and neutropenic fever was observed [4]. Therefore, alternative topotecan dosing schedules are being evaluated in several studies. One such strategy has been the development of weekly dosing schedules. Weekly administration of topotecan at a dose of 4 mg/m^2 has been uniformly confirmed to be less toxic but as effective as the 5-day regimen in multiple Phase II studies [4]. However, racial disparity may exist in terms of treatment response and toxicity. A previous study evaluated racial disparities in treatment toxicity among patients with advanced EOC and found that black women had significantly less Grade 3/4 leukopenia and gastrointestinal toxicity than Caucasian women [5]. Therefore, there is an urgent need to evaluate whether this alternative dosing schedule is safe in a Taiwanese population. In this study, we attempted to provide our experience of using weekly topotecan for the treatment of heavily pretreated recurrent EOC and PPC and to investigate the safety and efficacy of this type of alternative dosing.

Materials and methods

We retrospectively reviewed the medical records of patients with recurrent EOC and PPC who had been treated with weekly topotecan at the Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hospital, Taiwan, between November 2008 and May 2012. A total of 37 patients were identified initially; however, five patients discontinued treatment for personal reasons after receiving only one or two courses of weekly topotecan. These patients were considered to be unsuitable candidates for efficacy and safety evaluation and were excluded. Finally, a total of 32 patients were eligible for this study. All of them had previously been exposed to at least one regimen of platinum-based chemotherapy, and had an acceptable performance status [Eastern Cooperative Oncology Group (ECOG) $\leq$ 2]. Patients were categorized as having platinum-sensitive disease (a relapse-free interval of longer than 6 months after primary therapy) or platinum-resistant disease (relapse within 6 months). All the patients had elevated cancer antigen-125 (CA-125) levels or clinically measurable disease as well as adequate bone marrow, hepatic, and renal function before treatment. Tumor response could be evaluated either serologically using the change in CA-125 level or by radiologic signs of regression or progression.

Topotecan was administered at a dosage ranging between 2.75 mg/m^2 and 4 mg/m^2 every week via a 30-minute IV infusion on Days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity occurred. The initial dose was chosen according to the patient's performance status, general medical condition, the number of previous chemotherapy regimens pretreated, or physicians' preference. All patients had a CA-125 level evaluation every 4 weeks, and an imaging study was arranged in some cases for patients as indicated. All patients were assessed for toxicity based on the National Cancer Institute Common Toxicity Criteria (CTC) and tumor response according to Gynecologic Cancer Inter Group (GCIG) criteria for change in serum CA-125 level [6]. Briefly, two pretreatment serum measurements at least twice ($\geq$ 70 U/mL) the upper limit of normal (ULN) (> 35 U/mL) and at least two additional serum measurements after the start of treatment were required to have assessable disease. A 50% reduction of the pretreatment serum CA-125 level that was sustained over 28 days indicated a response. A complete response (CR) was defined as a reduction in CA-125 below the ULN that was sustained for at least 28 days. Otherwise, patients meeting the response criteria were classified as having partial responses (PRs). Progression was defined as a two-fold increase in the ULN if the nadir value was less than the ULN or a two-fold increase in the nadir value if the nadir value was greater than the ULN or death. Response Criteria in Solid Tumors (RECIST v1.1) was also applied in patients with measurable disease [7]. Briefly, a CR was defined as complete disappearance of all measurable disease; a PR was documented in patients with a greater than 50% decrease in the size of measurable lesions; stable disease (SD) was defined as a reduction of less than 50% or an increase of less than 25% in the tumor lesion; and progressive disease (PD) was defined as an increase of more than 25% in the tumor lesion compared with the status before treatment. Progression-free survival (PFS) was calculated as the period from the treatment initiation to the time of documented progression. Overall survival (OS) was measured as the period from the first day of topotecan treatment to death or the date of analysis. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital.

Statistical analysis

The significance of the difference in percentage was calculated using a χ^2/Fisher's exact test. PFS and OS analyses were calculated by the Kaplan–Meier method. A p value of less than 0.05 was required for statistical significance. Data processing and statistical analysis was performed using the Statistical Package for Social Sciences software package (version 17 for Windows; SPSS Inc., Chicago, IL, USA).

Results

All the 32 patients were eligible for treatment evaluation. The characteristics of our patients are outlined in Table 1. The median age was 58 years (range 29–83 years). Most patients had serous histology (68.8%) and an ECOG performance status of 0 (65.6%). The majority of patients (81.3%) had International Federation of Gynecology and Obstetrics (FIGO) Stage III or Stage IV disease at initial diagnosis. Most of the patients (75%) had received at least two previous regimens of chemotherapy. Twenty (62.5%) had platinum-sensitive disease while 12 (37.5%) had platinum-resistant disease. For 29 patients (90.6%) with elevated CA-125 levels at the start of weekly topotecan treatment, we used GCIG criteria for evaluation of the treatment response. For the other three patients (9.4%) with normal serum CA-125 levels, but obvious morphologic evidence of disease recurrence (liver or lung metastasis confirmed by computed tomography or palpable neck metastatic lymph node), we adopted RECIST for response determination. Overall, 318 courses of weekly topotecan were administered, with a median number of seven courses per patient (range 3–45 courses). A dose of 4 mg/m^2, 3.5 mg/m^2, and 2.75 mg/m^2 was given in 20, five, and seven patients, respectively. There were no differences in patient characteristics among the groups receiving different topotecan dose intensities (Table 2).

Table 3 shows the treatment response in relation to different clinical characteristics. The median PFS was 3 months [95% confidence interval (CI) 2.7–3.2]. Ten of the 32 patients (31.3%) are still alive with disease at the time of analysis with a median OS of 20 months (95% CI 11.1–28.9) (Fig. 1A,B). The overall response rate (ORR) was 21.9% (7 of 32 patients). No patients experienced a CR. Seven patients (21.9%) had a PR, SD was observed in 7 patients (21.9%), and PD occurred in 18 patients (56.2%). No deaths were attributable to therapy. Of the 20 patients with platinum-sensitive

Table 1
Baseline clinical characteristics of patients.

Characteristic	Number of patients (%)
Median age (y)	58 (range 29–83)
Epithelial ovarian cancer	30 (93.8)
Primary peritoneal cancer	2 (6.2)
Histologic type	
Serous	22 (68.8)
Mucinous	1 (3.1)
Endometrioid	4 (12.5)
Clear cell	3 (9.4)
Undifferentiated carcinoma	2 (6.3)
ECOG performance status	
0	21 (65.6)
1	7 (21.9)
2	4 (12.5)
FIGO stage	
I	3 (9.4)
II	2 (6.3)
III	22 (68.8)
IV	4 (12.5)
Unstaged	1 (3.1)
Previous chemotherapy regimens	
1	8 (25.0)
2	14 (43.8)
3	4 (12.5)
4 or more	6 (18.7)
Platinum sensitivity	
Sensitive	20 (62.5)
Resistant	12 (37.5)
CA-125 level before therapy (U/mL)	
≤ 35	3 (9.4)
> 35	29 (90.6)

disease, four patients had a PR (20.0%), six had SD (30.0%), and 10 had PD (50.0%). Of the 12 patients with platinum-resistant disease, three patients had a PR (25.0%), one had SD (8.3%), and eight had PD (66.6%). No significant difference was observed between these two groups of patients in terms of PR and clinical benefit rate (PR + SD). The ORR for patients with different numbers of previous chemotherapy regimens was similar (25% and 20.8%). However, we found a favorable ORR (71.4%) in patients who received the lowest dose intensity (2.75 mg/m^2), although no survival benefit was observed (Fig. 1C). Because of the similarity in patient characteristics, the better response in the low-dose group was not related to more favorable clinical characteristics such as low stage, more platinum-sensitive disease, or fewer previous chemotherapy treatments.

Table 2
Clinical characteristics of the three groups using different doses.

Characteristic	Topotecan dosage (mg/m^2)		
	4, $n = 20$ (%)	3.5, $n = 5$ (%)	2.75, $n = 7$ (%)
ECOG performance status			
0	13 (65)	3 (60)	5 (71)
1	4 (20)	2 (40)	1 (14)
2	3 (15)	0 (0)	1 (14)
FIGO stage			
I	2 (10)	0 (0)	1 (14)
II	1 (5)	0 (0)	1 (14)
III	16 (80)	5 (100)	2 (29)
IV	1 (5)	0 (0)	3 (43)
Previous chemotherapy regimens			
1	5 (25)	1 (20)	2 (29)
2	10 (50)	2 (40)	2 (29)
3	3 (15)	0 (0)	1 (14)
4 or more	2 (10)	2 (40)	2 (29)
Platinum sensitivity			
Sensitive	12 (60)	4 (80)	4 (57)
Resistant	8 (40)	1 (20)	3 (43)

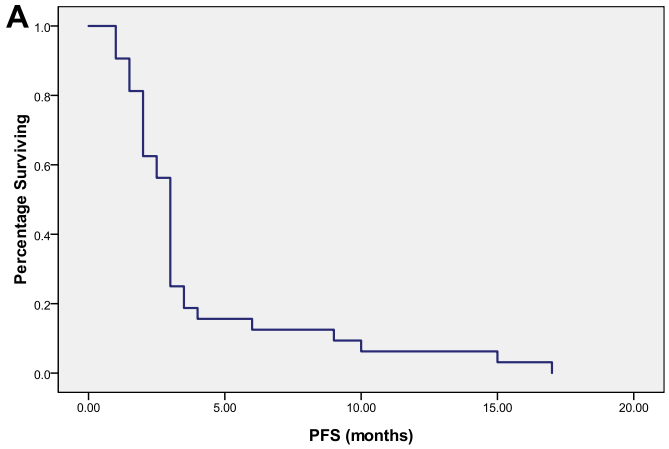
Table 3
Clinical response in relation to different clinical characteristics ($N = 32$).

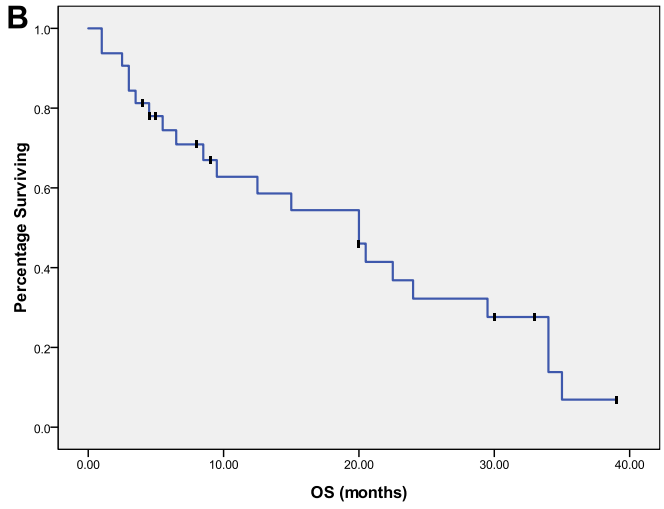
Characteristic			p
Courses of chemotherapy, median (range)		7 (3–45)	
Overall clinical response			
Complete response (CR)		0 (0%)	
Partial response (PR)		7 (21.9%)	
Stable disease (SD)		7 (21.9%)	
Progressive disease (PD)		18 (56.2%)	
Platinum-sensitivity			0.292
Sensitive ($n = 20$)			
PR		4 (20.0%)	
SD		6 (30.0%)	
PR + SD		10 (50.0%)	
Resistant ($n = 12$)			
PR		3 (25.0%)	
SD		1 (8.3%)	
PR + SD		4 (33.3%)	
Topotecan dosage, mg/m^2			0.001
4 ($n = 20$)	PR	2 (10%)	
	SD	3 (15%)	
3.5 ($n = 5$)	PR	0 (0%)	
	SD	3 (60.0%)	
2.75 ($n = 7$)	PR	5 (71.4%)	
	SD	1 (14.3%)	
Previous chemotherapy regimens			0.386
1 ($n = 8$)	PR	2 (25.0%)	
	SD	3 (37.5%)	
≥ 2 ($n = 24$)	PR	5 (20.8%)	
	SD	4 (16.7%)	

Table 4 shows the major adverse effects in terms of dose intensity and the number of previous chemotherapy treatment regimens. Overall, Grade 3/4 neutropenia was observed in six patients (18.8%). Grade 3/4 anemia and thrombocytopenia occurred in seven (21.9%) and two (6.2%) patients, respectively. Two patients developed neutropenic fever, which was transient and manageable with supportive care. Five patients received colony-stimulating factors for bone marrow support, while seven patients received blood transfusions for anemia. No patient withdrew from treatment due to toxicity. The most common nonhematologic toxicities were fatigue and nausea/vomiting. However, most nonhematologic toxicities were mild with only one (3.1%) patient experienced Grade 3 vomiting. Our results also suggested a more favorable toxicity profile in patients who had received the lowest dose intensity (2.75 mg/m^2) and only one previous chemotherapy regimen.

Discussion

This study appears to be the first report investigating an Asian population of recurrent EOC and PPC treated with weekly topotecan. We demonstrated a comparable toxicity profile in a Taiwanese population to that observed in other Western countries using a topotecan dosage of 4 mg/m^2/wk. Homesley et al [8] were the first to assess optimal weekly topotecan dosage. In that study, the maximum tolerated and recommended dose was found to be 4 mg/m^2, and doses below 2 mg/m^2 lacked antitumor activity. Later, several Phase II studies universally using 4 mg/m^2/wk IV bolus showed a similar response rate of 15–20% and Grade 3/4 neutropenia in 15–20% of patients with recurrent EOC/PPC [9–15]. It is interesting that our study also provided information that weekly topotecan administration at the lowest dose intensity of 2.75 mg/m^2 exhibited a more favorable efficacy. Moreover, no Grade 3/4 toxicity was found in this dosing group. However, due to the paucity of large sample sizes, further study is needed to provide strong evidence of more safety without compromising the therapeutic index of weekly topotecan in the lower dosing population. In





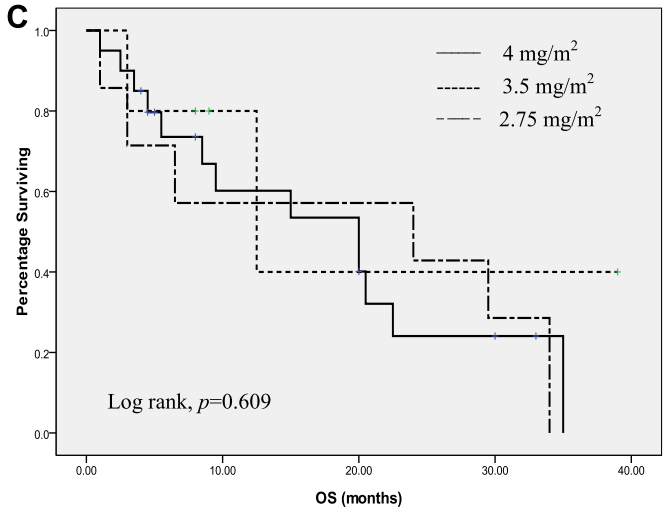


Fig. 1. (A) Progression-free survival (PFS). (B) Overall survival (OS). (C) There was no significant difference with regard to OS among those receiving different dose intensities of weekly topotecan.

addition, our response rate for the platinum-sensitive group (21.0%) was equivalent to the platinum-resistant group (23.1%), which was quite different to that of previous results. Reasons for this may include the fact that all the patients in the platinum-sensitive group had received platinum-based chemotherapy retreatment at first relapse. Thus patients in the platinum-sensitive group were more heavily pretreated than those in the platinum-resistant group in our study. The greater the number of chemotherapy pretreatments, the greater the chance that tumor cells would develop resistance [16].

Table 4
Comparison of major toxicity (Grade 3/4) at different dose intensities and different number of previous chemotherapy regimens.

	Overall toxicity	Topotecan dosage (mg/m^2)			Number of previous chemotherapy regimens	
	$N = 32$ (%)	4	3.5	2.75	1	≥ 2
		$n = 20$ (%)	$n = 5$ (%)	$n = 7$ (%)	$n = 8$ (%)	$n = 24$ (%)
Hematologic						
Leukopenia	4 (12.5)	2 (10)	2 (40)	0 (0)	0 (0)	4 (16.7)
Neutropenia	6 (18.8)	4 (20)	2 (40)	0 (0)	1 (12.5)	5 (20.8)
Anemia	7 (21.9)	7 (35)	0 (0)	0 (0)	1 (12.5)	6 (25.0)
Thrombocytopenia	2 (6.2)	1 (5)	1 (20)	0 (0)	0 (0)	2 (8.3)
Nonhematologic						
Fatigue	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea/vomiting	1 (3.1)	1 (5)	0 (0)	0 (0)	0 (0)	1 (4.1)

Although weekly topotecan can improve the toxicity profile without compromising antitumor activity in several Phase II trials, studies directly comparing weekly and conventional protocols are still limited. Largillier et al [17] were the first to report their experience of using two different types of dosing retrospectively. They found a significantly higher percentage of Grade 3/4 hematologic toxicities in the conventional arm including neutropenia (95.8% vs. 33.3%), anemia (37.5% vs. 9.5%), and thrombocytopenia (33.3% vs. 4.8%). However, there were no significant differences in terms of treatment response and OS. Later, both the Gynecologic Oncology Group (GOG) and the North Eastern German Society of Gynecological Oncology (NOGGO) conducted prospective trials comparing the conventional with the weekly schedule of topotecan [18,19]. In contrast to the previous retrospective study, the results of the two prospective trials showed less activity with weekly topotecan dosing. The response rates in the conventional versus weekly regimens in GOG and NOGGO trials were 27% versus 12% and 19% versus 9%, respectively. In the NOGGO trial, conventional dosing improved PFS (marginal significance) but not OS. In the GOG trial, the accrual on the conventional arm was insufficient and thus the survival data could not be analyzed. However, both prospective trials showed a hematologic toxicity profile in favor of weekly dosing. Therefore, both studies concluded that with regard to effectiveness in terms of response and PFS, conventional dosing remains the standard of care in patients with recurrent EOC. However, comparable OS rates and a favorable toxicity profile make weekly dosing an acceptable alternative in this setting.

An added benefit of the weekly IV bolus schedule is its greater convenience when compared with the conventional 5-day regimen. Also, weekly dosing may allow clinicians to monitor patients more frequently. Moreover, the improved hematologic toxicity profile of the weekly dosing may allow greater tolerability in combining topotecan with other antitumor agents such as gemcitabine [20], docetaxel [21], paclitaxel [22], or carboplatin [23]. Recently, weekly topotecan had been investigated to combine with the targeted agents such as bevacizumab [24], sorafenib [25], or lapatinib [26]. Of these, a weekly topotecan and biweekly bevacizumab combination demonstrated acceptable toxicity with the clinical benefit (PR + SD) rate approaching 60%. This promising result might be the potential synergistic anti-angiogenic effects of both agents [27], and their nonoverlapping toxicity profiles.

In conclusion, we demonstrated that weekly topotecan IV bolus was also well tolerated in a heavily pretreated Taiwanese

population with recurrent EOC and PPC. Our results further suggested that patients who received the lowest dose intensity (2.75 mg/m^2) appeared to gain substantial clinical benefits and a better toxicity profile. Further investigation of this dosage with more patients is warranted to confirm this finding.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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